PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WO3100-dV jdh		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00102	17/02/2000	18/02/1999
International Patent Classification (IPC) or national classification and IPC A61B5/028		
Applicant JANSEN, Jozef, Reinier, Cornelis et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/09/2000	30.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fontenay, P Telephone No. +49 89 2399 2646

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00102

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-8 as originally filed

Claims, No.:

1-7 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: EN , which is:

- ☒ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☒ the language of publication of the international application (under Rule 48.3(b)).
- ☒ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☒ the claims, Nos.: 6. 7

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-3.

because:

☒ the said international application, or the said claims Nos. 1-3 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 4, 5

	No:	Claims	
Inventive step (IS)	Yes:	Claims	4, 5
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	4, 5
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 The claims 1-3 refer to a method for determining the cardiac output and comprise the step of injecting an indicator into the patient's bloodstream. The claimed method is accordingly surgical nature and is considered to refer to subject-matter for which no IPER has to be drawn by the IPEA (Rule 67.1 (iv) PCT).

Re Item V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:
D1: EP-A-374248
D2: US-A-4819655

The document D1 was not cited in the international search report.

V.1 The subject-matter of claim 4 is new and inventive in the sense of Article 33(2) and 33(3) PCT.

D1 which is assumed to illustrate the closest prior art as to the subject-matter of claim 4 discloses an apparatus for determining the cardiac output of a patient (see D1, page 52, lines 3-20). The apparatus disclosed in D1 comprises a control output for controlling injection means and a first sensor for measuring the change in an indicator value in the patient's bloodstream (see D1, page 35, lines 12-23). In D1, the processing unit is arranged for measuring the change in the indicator value in the bloodstream downstream of the injection point, establishing the injected amount of indicator injected into the blood and the initial value thereof.

The subject-matter of claim 4 differs from said known apparatus in that it comprises a sensor for determining the patient's respiration cycle and in that the processing unit is arranged for measuring a first variation and a second variation of the temperature of the blood over respectively at least one respiration cycle

prior to and contiguous to the injection and in that it determines the change in the indicator value resulting from the injection on the basis of the difference between the measured change in the indicator value measured over a period of n cycles and n times the measured first variation.

The problem solved is to provide more accurate results as to the CO taking into account the pulsatile nature of the measured Cardiac Output and possible temperature drifts of the body temperature.

Since D2 relates to similar methods and devices for determining CO by dilution techniques, its teaching would be taken into account by the skilled man looking for a solution to the above problem. It is suggested in D2 (see column 6, lines 7-20) to consider values average over a plurality of respiratory cycles which implies the presence of a respiratory sensor. However, D2 does not contain any indication as to a first measurement before injection and a second one contiguous to the injection in order to take into account possible drifts in the body temperature.

It follows that the subject-matter of claim 4 would not be obvious for the skilled man when considering the teaching of both documents D1 and D2.

V.2 Claim 5 refers to a preferred embodiment of the apparatus for measuring the cardiac output according to claim 4. The subject-matter of claim 4 being considered as new and inventive, the same applies to said preferred embodiment.

Re Item VIII Certain observations on the international application

VIII.1 The subject-matter of claim 4 as to the apparatus is not clearly defined contrary to the requirements of Article 6 PCT.

The terminology employed in the present application in relation with the term "indicator" is confusing. The fact that the processing unit is arranged for measuring a first variation of the indicator value preferably directly prior to the injection of indicator would suggest that said indicator also relates to a substance already present in the blood. However in the case of a cold fluid as suggested for

example on page 4, line 36, of the description, this definition leads to a certain confusion. It is in particular not clear how such a cold fluid could be measured before it has been introduced.

Insertion page to be inserted on page 2, line 24.

EP-A-0 374 248 discloses an apparatus for determining the cardiac output of a patient, comprising a control output for controlling injection means and a first sensor for measuring the change in an indicator value in the patient's bloodstream. A processing unit is arranged for measuring the change in the indicator value in the bloodstream downstream of the injection point, establishing the injected amount of indicator injected into the blood and the initial value thereof.

US-A-4 819 655 discloses a method and apparatus for determining cardiac output, wherein the cardiac output is determined by measuring the blood temperature over a period of one or two respiratory cycles prior to injection of the indicator and measuring the change in blood temperature over the same period of time after injection of the indicator.

temperature change is marked off as a function of the time. The average cardiac output is measured by one controlled injection for the duration of a respiration cycle and it is not necessary to carry out a number of measurements. In the example of Figure 2 the period during which the change in the concentration is recorded is indicated T1. This period runs from 6=4 to 6=12.

When a cold fluid is injected as the indicator, the following equation applies:

$$Q_i \rho_i S_i (T_b - T_i) = Q'_b \rho_b S_b \int \Delta T_b(t) dt$$

wherein Q_i is the injected volume, ρ is the specific heat and S is the specific mass of (i) injected matter and (b) blood, respectively, T is the temperature, Q'_b is the cardiac output and ΔT_b is the change in the temperature of the blood brought about by the injection of cold fluid.

Rearrangement of the formula shows how the cardiac output can be computed.

$$Q'_b = Q_i \frac{\rho_i S_i (T_b - T_i)}{\rho_b S_b \int \Delta T_b(t) dt}$$

This formula forms the basis for most thermal dilution "cardiac output" computers.

Research has shown that it is not possible to achieve accurate measuring results in this manner, since the pulsating cardiac output fluctuates due to the natural respiration or artificial respiration via a ventilator. This is schematically shown in Figure 2. In this case the temperature change also includes a temperature variation which is not caused by the injection. This influence on the respiration can be removed by measuring the area below the measured temperature curve over a period of exactly one respiration cycle, preferably directly prior to the injection of the cold fluid. In the embodiment as shown in Figure 2 injection takes place at t=4, and consequently area A is measured first for the duration of period T2. The determination of area B under the temperature

curve is started at the time of injection t=4, and lasts over a period of a number n of respiration cycles until t=12. The area resulting from the injection of the cold fluid will then be Area-Dil = B - n x A.

The cardiac output is then computed as:

$$Q'_b = Q_i \frac{\rho_i S_i (T_b - T_i)}{\rho_b S_b \; Area - Dil}$$

The influence of slow temperature drift resulting from an increase or decrease of the body temperature, for example, can furthermore be eliminated by measuring the temperature change over a period of exactly one respiration cycle directly prior to as well as directly contiguous to the injection. This situation is shown in Figure 3. Both area A and area C are thereby measured over period T2 and over period T3, respectively, so that the area resulting from the injection of the cold fluid will then be Area-Dil = B - n/2 x (A + C).

It is therefore possible with the method and apparatus disclosed herein to measure the average cardiac output of a patient with great accuracy by means of only one injection of indicator.

According to a very advantageous embodiment the apparatus is also fitted with a sensor 12, which is connected to the processing unit 1 via an amplifier 13. Sensor 12 measures the arterial blood pressure signal, for example in the aorta. It is known per se that it is possible to compute the noncalibrated value of the stroke volume and the cardiac output from said arterial blood pressure signal over a period of one pulsation of the heart. This is for example disclosed in US-A-3 841 313. In the apparatus disclosed therein, the computed values of the cardiac output are recorded over the period of the measurement of the thermal dilution curve, and the average thereof is determined. Then a proportionality constant is computed by the processing unit 1 by comparing the cardiac output value thus computed with the cardiac output which has been determined by means of the thermal dilution method. Then the computed values

[by means of a controlled injection means (3)]

CLAIMS

1. A method for determining the cardiac output of a patient, wherein the patient's respiration cycle is determined and an indicator is injected [...] into the patient's bloodstream over a period of at least substantially one respiration cycle, wherein the change in the indicator value in the bloodstream downstream of the injection point is measured over a period (T_1) of a number (n) of respiration cycles and the injected amount of indicator is established, wherein the cardiac output is determined on the basis of the measured change in the indicator value, the amount of indicator injected into the blood and the initial value thereof, characterized in that a first variation in the indicator value is measured over at least substantially ~~the~~ a period (T_2) of one respiration cycle, preferably directly prior to the injection, <...> and in that the change in the indicator value caused by the injection is determined on the basis of the difference between the change in the indicator value measured over a period (T_1) of n times the period that of the first variation and n times (the average of the) measured first (and second) variations.

~~2. A method according to claim 1, wherein~~ a second (T_2) variation in the indicator value is measured over a period of at least substantially one respiration cycle, preferably directly contiguous to the measurement of the change in the indicator value, wherein the average of the first and the second variation is determined, ~~which average is used for determining the change in the indicator value rather than the first variation.~~

2. A method according to claim 1 ~~or 2~~, wherein the arterial blood pressure signal is measured, wherein the values of the stroke volume and of the cardiac output over a period of one heartbeat are calculated over a period corresponding to the number (n) of respiration cycles, wherein the average of the calculated values is determined, and wherein a proportionality constant is computed from a comparison of the average output value thus calculated and the cardiac output value determined on the basis of the change in the indicator value, after which the stroke volume and the cardiac output are multiplied by the

computed proportionality constant.

3. A method according to claim 2, wherein the determination of the cardiac output from the change in the indicator value is repeated periodically by carrying out a new injection and computing the proportionality constant.

4. Apparatus for determining the cardiac output of a patient, which apparatus comprises a processing unit (1) having a control output (2) for controlling injection means (3), a first sensor (7) for measuring the change in an indicator value in the patient's bloodstream and a second sensor (10) for determining the patient's respiration cycle, wherein the processing unit is arranged for measuring the change in the indicator value in the bloodstream downstream of the injection point over a number (n) of respiration cycles, establishing the injected amount of indicator and determining the cardiac output on the basis of the measured change in the indicator value, the amount of indicator injected into the blood and the initial value thereof, characterized in that the processing unit (1) is arranged for measuring a first variation of the indicator value over a period (T_2) of at least substantially one respiration cycle, preferably directly prior to the injection of indicator, and the processing unit is arranged for determining the change in the indicator value resulting from the injection on the basis of the difference between the measured change in the indicator value measured over a period (T_1) of n times ~~that~~ the period of the first variation and n times (the average of the measured first and second) variations.

~~5. Apparatus according to claim 5, wherein the processing unit is arranged~~ for measuring a second variation in the indicator value ~~is measured~~ over a period (T_3) of at least substantially one respiration cycle, preferably directly contiguous to the measurement of the change in the indicator value, wherein the processing unit determines the average of the first and the second variation, ~~which average is used for determining the change in the indicator value rather than the first variation~~.

5. Apparatus according to claim ~~5 or 6~~ 4 comprising a third sensor (12) for measuring an arterial blood pressure signal, wherein the processing unit (1) is arranged for calculating the values of the stroke volume and of the cardiac output over a

period of one heartbeat over a period corresponding to the number (n) of respiration cycles, wherein the average of the calculated values is determined, wherein the processing unit compares the average cardiac output value thus calculated and the cardiac output value determined on the basis of the change in the indicator value and computes a proportionality constant, after which the processing unit multiplies the stroke volume and the cardiac output computed from the arterial blood pressure signal by the computed proportionality constant.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
W03100-dV		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/NL 00/ 00102	17/02/2000	18/02/1999
Applicant		
JANSEN, Jozef, Reinier, Corn et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL 00/00102

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

[redacted]tional Application No
PCT/NL 00/00102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/028

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 819 655 A (WEBLER) 11 April 1989 (1989-04-11) column 3, line 60 -column 7, line 65	5-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2000	07/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lemercier, D

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/NL 00/00102

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4819655 A	11-04-1989	NONE	

INTERNATIONAL SEARCH REPORT

Inter. Application No
PCT/NL 00/00102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/028

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 819 655 A (WEBLER) 11 April 1989 (1989-04-11) column 3, line 60 -column 7, line 65	5-7

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2000	07/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lemercier, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/NL 00/00102

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4819655 A	11-04-1989	NONE	

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61B 5/028

A1

(11) International Publication Number: WO 00/53087

(43) International Publication Date: 14 September 2000 (14.09.00)

(21) International Application Number: PCT/NL00/00102

(22) International Filing Date: 17 February 2000 (17.02.00)

(30) Priority Data:
1011339 18 February 1999 (18.02.99) NL

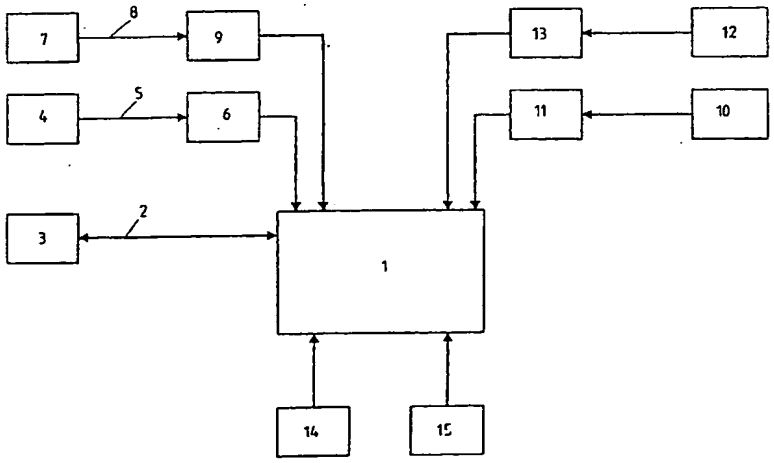
(71)(72) Applicants and Inventors: JANSEN, Jozef, Reinier, Cornelis [NL/NL]; Aster 8, NL–2211 MZ Noordwijkerhout (NL). SCHREUDER, Johannes, Jacobus [NL/IT]; Via Eleonora Duse, 32, I–21100 Varese (IT).

(74) Agent: DE VRIES, Johannes, Hendrik, Fokke; De Vries & Metman B.V., Overschiestraat 180, NL–1062 XK Amsterdam (NL).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
In English translation (filed in Dutch).

(54) Title: METHOD AND APPARATUS FOR DETERMINING THE CARDIAC OUTPUT OF A PATIENT



(57) Abstract

In order to determine the cardiac output of a patient, the patient's respiration cycle is determined and an indicator is injected into the patient's bloodstream over a period of at least substantially one respiration cycle. The change in the indicator value in the bloodstream downstream of the injection point is measured over a period of a number (n) of respiration cycles and the injected amount of indicator is established. The cardiac output is determined on the basis of the measured change in the indicator value, the injected amount of indicator blood and the initial value thereof. To this end a first variation in the indicator value is measured over at least substantially the period of one respiration cycle, directly prior to the injection, and the change in the indicator value caused by the injection is determined on the basis of the difference between the measured change in the indicator value measured over a period of n times that of the first variation and n times the measured first variation.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/NL 00/00102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/028

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 819 655 A (WEBLER) 11 April 1989 (1989-04-11) column 3, line 60 -column 7, line 65	5-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 2000	07/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lemercier, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

..formation on patent family members

Inter nal Application No
PCT/NL 00/00102

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4819655 A	11-04-1989	NONE	

09/913597

PATENT COOPERATION TREATY

REC'D 14. 08. 01
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WO3100-dV jdh		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL00/00102	17/02/2000	18/02/1999
International Patent Classification (IPC) or national classification and IPC A61B5/028		
Applicant JANSEN, Jozef, Reinier, Cornelis et al.		

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TECHNOLOGY CENTER R3700

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/09/2000	30.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fontenay, P Telephone No. +49 89 2399 2646

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00102

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1,3-5,8	as originally filed	
2,6,7	with telefax of	07/03/2001

Claims, No.:

1-5	with telefax of	07/03/2001

Drawings, sheets:

1/3-3/3	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: EN , which is:

   - ☒ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☒ the language of publication of the international application (under Rule 48.3(b)).
   - ☒ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:

☒ the claims, Nos.: 6. 7

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-3.

because:

☒ the said international application, or the said claims Nos. 1-3 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 4, 5
	No:	Claims
Inventive step (IS)	Yes:	Claims 4, 5
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 4, 5
	No:	Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 The claims 1-3 refer to a method for determining the cardiac output and comprise the step of injecting an indicator into the patient's bloodstream. The claimed method is accordingly surgical nature and is considered to refer to subject-matter for which no IPER has to be drawn by the IPEA (Rule 67.1 (iv) PCT).

Re Item V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:
D1: EP-A-374248
D2: US-A-4819655

The document D1 was not cited in the international search report.

V.1 The subject-matter of claim 4 is new and inventive in the sense of Article 33(2) and 33(3) PCT.

D1 which is assumed to illustrate the closest prior art as to the subject-matter of claim 4 discloses an apparatus for determining the cardiac output of a patient (see D1, page 52, lines 3-20). The apparatus disclosed in D1 comprises a control output for controlling injection means and a first sensor for measuring the change in an indicator value in the patient's bloodstream (see D1, page 35, lines 12-23). In D1, the processing unit is arranged for measuring the change in the indicator value in the bloodstream downstream of the injection point, establishing the injected amount of indicator injected into the blood and the initial value thereof.

The subject-matter of claim 4 differs from said known apparatus in that it comprises a sensor for determining the patient's respiration cycle and in that the processing unit is arranged for measuring a first variation and a second variation of the temperature of the blood over respectively at least one respiration cycle

prior to and contiguous to the injection and in that it determines the change in the indicator value resulting from the injection on the basis of the difference between the measured change in the indicator value measured over a period of n cycles and n times the measured first variation.

The problem solved is to provide more accurate results as to the CO taking into account the pulsatile nature of the measured Cardiac Output and possible temperature drifts of the body temperature.

Since D2 relates to similar methods and devices for determining CO by dilution techniques, its teaching would be taken into account by the skilled man looking for a solution to the above problem. It is suggested in D2 (see column 6, lines 7-20) to consider values average over a plurality of respiratory cycles which implies the presence of a respiratory sensor. However, D2 does not contain any indication as to a first measurement before injection and a second one contiguous to the injection in order to take into account possible drifts in the body temperature.

It follows that the subject-matter of claim 4 would not be obvious for the skilled man when considering the teaching of both documents D1 and D2.

V.2 Claim 5 refers to a preferred embodiment of the apparatus for measuring the cardiac output according to claim 4. The subject-matter of claim 4 being considered as new and inventive, the same applies to said preferred embodiment.

Re Item VIII Certain observations on the international application

VIII.1 The subject-matter of claim 4 as to the apparatus is not clearly defined contrary to the requirements of Article 6 PCT.

The terminology employed in the present application in relation with the term "indicator" is confusing. The fact that the processing unit is arranged for measuring a first variation of the indicator value preferably directly prior to the injection of indicator would suggest that said indicator also relates to a substance already present in the blood. However in the case of a cold fluid as suggested for

example on page 4, line 36, of the description, this definition leads to a certain confusion. It is in particular not clear how such a cold fluid could be measured before it has been introduced.

Insertion page to be inserted on page 2, line 24.

EP-A-0 374 248 discloses an apparatus for determining the cardiac output of a patient, comprising a control output for controlling injection means and a first sensor for measuring the change in an indicator value in the patient's bloodstream. A processing unit is arranged for measuring the change in the indicator value in the bloodstream downstream of the injection point, establishing the injected amount of indicator injected into the blood and the initial value thereof.

US-A-4 819 655 discloses a method and apparatus for determining cardiac output, wherein the cardiac output is determined by measuring the blood temperature over a period of one or two respiratory cycles prior to injection of the indicator and measuring the change in blood temperature over the same period of time after injection of the indicator.

temperature change is marked off as a function of the time. The average cardiac output is measured by one controlled injection for the duration of a respiration cycle and it is not necessary to carry out a number of measurements. In the example of Figure 2 the period during which the change in the concentration is recorded is indicated T1. This period runs from 6=4 to 6=12.

When a cold fluid is injected as the indicator, the following equation applies:

$$Q_i \rho_i S_i (T_b - T_i) = Q'_b \rho_b S_b \int \Delta T_b(t) dt$$

wherein Q_i is the injected volume, ρ is the specific heat and S is the specific mass of (i) injected matter and (b) blood, respectively, T is the temperature, Q'_b is the cardiac output and ΔT_b is the change in the temperature of the blood brought about by the injection of cold fluid.

Rearrangement of the formula shows how the cardiac output can be computed.

$$Q'_b = Q_i \frac{\rho_i S_i (T_b - T_i)}{\rho_b S_b \int \Delta T_b(t) dt}$$

This formula forms the basis for most thermal dilution "cardiac output" computers.

Research has shown that it is not possible to achieve accurate measuring results in this manner, since the pulsating cardiac output fluctuates due to the natural respiration or artificial respiration via a ventilator. This is schematically shown in Figure 2. In this case the temperature change also includes a temperature variation which is not caused by the injection. This influence on the respiration can be removed by measuring the area below the measured temperature curve over a period of exactly one respiration cycle, preferably directly prior to the injection of the cold fluid. In the embodiment as shown in Figure 2 injection takes place at t=4, and consequently area A is measured first for the duration of period T2. The determination of area B under the temperature

curve is started at the time of injection t=4, and lasts over a period of a number n of respiration cycles until t=12. The area resulting from the injection of the cold fluid will then be Area-Dil = B - n x A.

The cardiac output is then computed as:

$$Q'_b = Q_i \frac{\rho_i S_i (T_b - T_i)}{\rho_b S_b \; Area - Dil}$$

The influence of slow temperature drift resulting from an increase or decrease of the body temperature, for example, can furthermore be eliminated by measuring the temperature change over a period of exactly one respiration cycle directly prior to as well as directly contiguous to the injection. This situation is shown in Figure 3. Both area A and area C are thereby measured over period T2 and over period T3, respectively, so that the area resulting from the injection of the cold fluid will then be Area-Dil = B - n/2 x (A + C).

It is therefore possible with the method and apparatus disclosed herein to measure the average cardiac output of a patient with great accuracy by means of only one injection of indicator.

According to a very advantageous embodiment the apparatus is also fitted with a sensor 12, which is connected to the processing unit 1 via an amplifier 13. Sensor 12 measures the arterial blood pressure signal, for example in the aorta. It is known per se that it is possible to compute the noncalibrated value of the stroke volume and the cardiac output from said arterial blood pressure signal over a period of one pulsation of the heart. This is for example disclosed in US-A-3 841 313. In the apparatus disclosed therein, the computed values of the cardiac output are recorded over the period of the measurement of the thermal dilution curve, and the average thereof is determined. Then a proportionality constant is computed by the processing unit 1 by comparing the cardiac output value thus computed with the cardiac output which has been determined by means of the thermal dilution method. Then the computed values

[by means of a controlled injection means (3)]

CLAIMS

1. A method for determining the cardiac output of a patient, wherein the patient's respiration cycle is determined and an indicator is injected into the patient's bloodstream over a period of at least substantially one respiration cycle, wherein the change in the indicator value in the bloodstream downstream of the injection point is measured over a period (T_1) of a number (n) of respiration cycles and the injected amount of indicator is established, wherein the cardiac output is determined on the basis of the measured change in the indicator value, the amount of indicator injected into the blood and the initial value thereof, characterized in that a first variation in the indicator value is measured over at least substantially ~~the~~ period (T_2) of one respiration cycle, preferably directly prior to the injection, and in that the change in the indicator value caused by the injection is determined on the basis of the difference between the change in the indicator value measured over a period (T_1) of n times ~~that~~ the period of the first variation and n times ~~the~~ (average of the) measured first (and second) variations.

~~2. A method according to claim 1, wherein~~ a second variation in the indicator value is measured over a period (T_2) of at least substantially one respiration cycle, preferably directly contiguous to the measurement of the change in the indicator value, wherein the average of the first and the second variation is determined, ~~which average is used for determining the change in the indicator value rather than the first variation.~~

2. A method according to claim 1 ~~or 2~~, wherein the arterial blood pressure signal is measured, wherein the values of the stroke volume and of the cardiac output over a period of one heartbeat are calculated over a period corresponding to the number (n) of respiration cycles, wherein the average of the calculated values is determined, and wherein a proportionality constant is computed from a comparison of the average output value thus calculated and the cardiac output value determined on the basis of the change in the indicator value, after which the stroke volume and the cardiac output are multiplied by the

computed proportionality constant.

3. A method according to claim 2, wherein the determination of the cardiac output from the change in the indicator value is repeated periodically by carrying out a new injection and computing the proportionality constant.

4. Apparatus for determining the cardiac output of a patient, which apparatus comprises a processing unit (1) having a control output (2) for controlling injection means (3), a first sensor (7) for measuring the change in an indicator value in the patient's bloodstream and a second sensor (10) for determining the patient's respiration cycle, wherein the processing unit is arranged for measuring the change in the indicator value in the bloodstream downstream of the injection point over a number (n) of respiration cycles, establishing the injected amount of indicator and determining the cardiac output on the basis of the measured change in the indicator value, the amount of indicator injected into the blood and the initial value thereof, characterized in that the processing unit (1) is arranged for measuring a first variation of the indicator value over a period (T_2) of at least substantially one respiration cycle, preferably directly prior to the injection of indicator, and the processing unit is arranged for determining the change in the indicator value resulting from the injection on the basis of the difference between the measured change in the indicator value measured over a period (T_1) of n times the period of the first variation and n times the average of the measured first and second variations.

~~5. Apparatus according to claim 5, wherein the processing unit is arranged~~ for measuring a second variation in the indicator value ~~is measured~~ over a period (T_3) of at least substantially one respiration cycle, preferably directly contiguous to the measurement of the change in the indicator value, wherein the processing unit determines the average of the first and the second variation, ~~which average is used for determining the change in the indicator value rather than the first variation.~~

6. Apparatus according to claim 4 comprising a third sensor (12) for measuring an arterial blood pressure signal, wherein the processing unit (1) is arranged for calculating the values of the stroke volume and of the cardiac output over a

period of one heartbeat over a period corresponding to the number (n) of respiration cycles, wherein the average of the calculated values is determined, wherein the processing unit compares the average cardiac output value thus calculated and the cardiac output value determined on the basis of the change in the indicator value and computes a proportionality constant, after which the processing unit multiplies the stroke volume and the cardiac output computed from the arterial blood pressure signal by the computed proportionality constant.

RECORD COPY

WO3100-dV

PCT REQUEST

Original (for **SUBMISSION**) - printed on 15.02.2000 09:51:46 AM

0 0-1	**For receiving Office use only** International Application No.	PCT/NL 00/00102
0-2	International Filing Date	17 FEB 2000 (17.02.00)
0-3	Name of receiving Office and "PCT International Application"	BUREAU VOOR DE INDUSTRIËLE EIGENDOM P.C.T. INTERNATIONAL APPLICATION
0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.90 (updated 01.01.2000)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Netherlands Industrial Property Office (RO/NL)
0-7	**Applicant's or agent's file reference**	WO3100-dV
I	**Title of invention**	METHOD AND APPARATUS FOR DETERMINING THE CARDIAC OUTPUT OF A PATIENT
II II-1 II-2 II-4 II-5 II-6 II-7	**Applicant** This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	 applicant and inventor all designated States JANSEN, Jozef, Reinier, Cornelis Aster 8 NL-2211 MZ NOORDWIJKERHOUT Netherlands NL NL
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Applicant and/or inventor** This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	 applicant and inventor all designated States SCHREUDER, Johannes, Jacobus Via Eleonora Duse 32 I-21100 VARESE Italy NL IT

PCT REQUEST

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IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	DE VRIES, Johannes, Hendrik, Fokke
IV-1-2	Address:	DE VRIES & METMAN B.V. Overschiestraat 180 NL-1062 XK AMSTERDAM Netherlands
IV-1-3	Telephone No.	+31 20 5110930
IV-1-4	Facsimile No.	+31 20 5110931
IV-1-5	e-mail	mail@dvme.nl
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AL AM AT AU AZ BA BB BG BR BY CA CH&LI CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

PCT REQUEST

Original (for **SUBMISSION**) - printed on 15.02.2000 09:51:46 AM

V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	**Exclusion(s) from precautionary designations**	NONE	
VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	18 February 1999 (18.02.1999)	
VI-1-2	Number	1011339	
VI-1-3	Country	NL	
VI-2	**Priority document request** The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VII-2	**Request to use results of earlier search; reference to that search**		
VII-2-1	Date	22 October 1999 (22.10.1999)	
VII-2-2	Number	SN 32662 NL	
VII-2-3	Country (or regional Office)	EP	
VIII	**Check list**	number of sheets	electronic file(s) attached
VIII-1	Request	4	-
VIII-2	Description	8	-
VIII-3	Claims	3	-
VIII-4	Abstract	1	abstract_wo3100.txt
VIII-5	Drawings	3	-
VIII-7	TOTAL	19	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-13	Translation of international application into:	English	
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	**Figure of the drawings which should accompany the abstract**	1	
VIII-19	**Language of filing of the international application**	Dutch	

PCT REQUEST

Original (for **SUBMISSION**) - printed on 15.02.2000 09:51:46 AM

IX-1	Signature of applicant or agent	
IX-1-1	Name (LAST, First)	DE VRIES, Johannes, Hendrik, Fokke

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10-1	Date of actual receipt of the purported international application	17 FEB 2000 (17.02.00)
10-2	Drawings:	
10-2-1	Received	Received
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	15 MARCH 2000 (15.03.00)

PCT/NL 00/00102

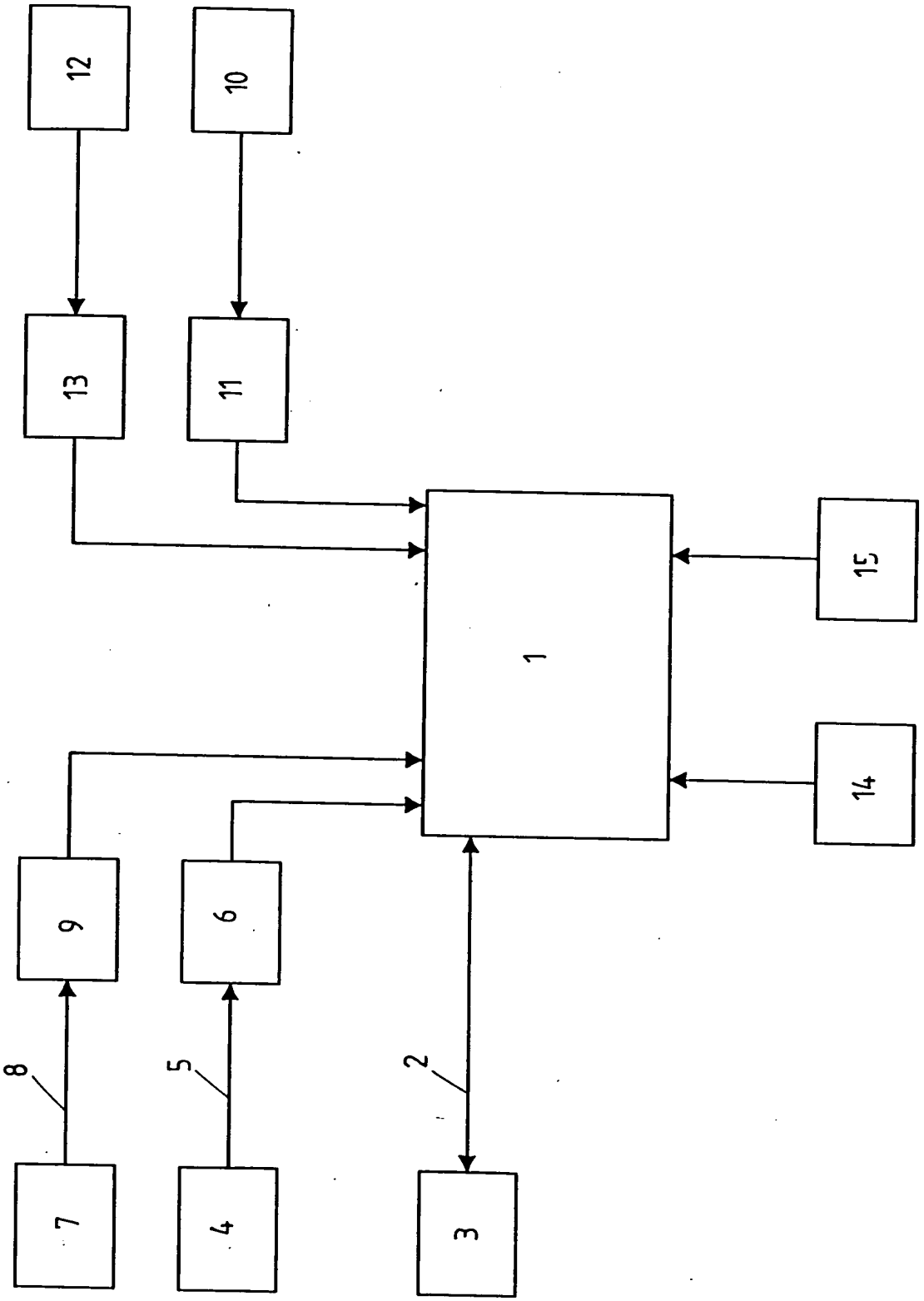

fig.1

PCT/NL 00/00102

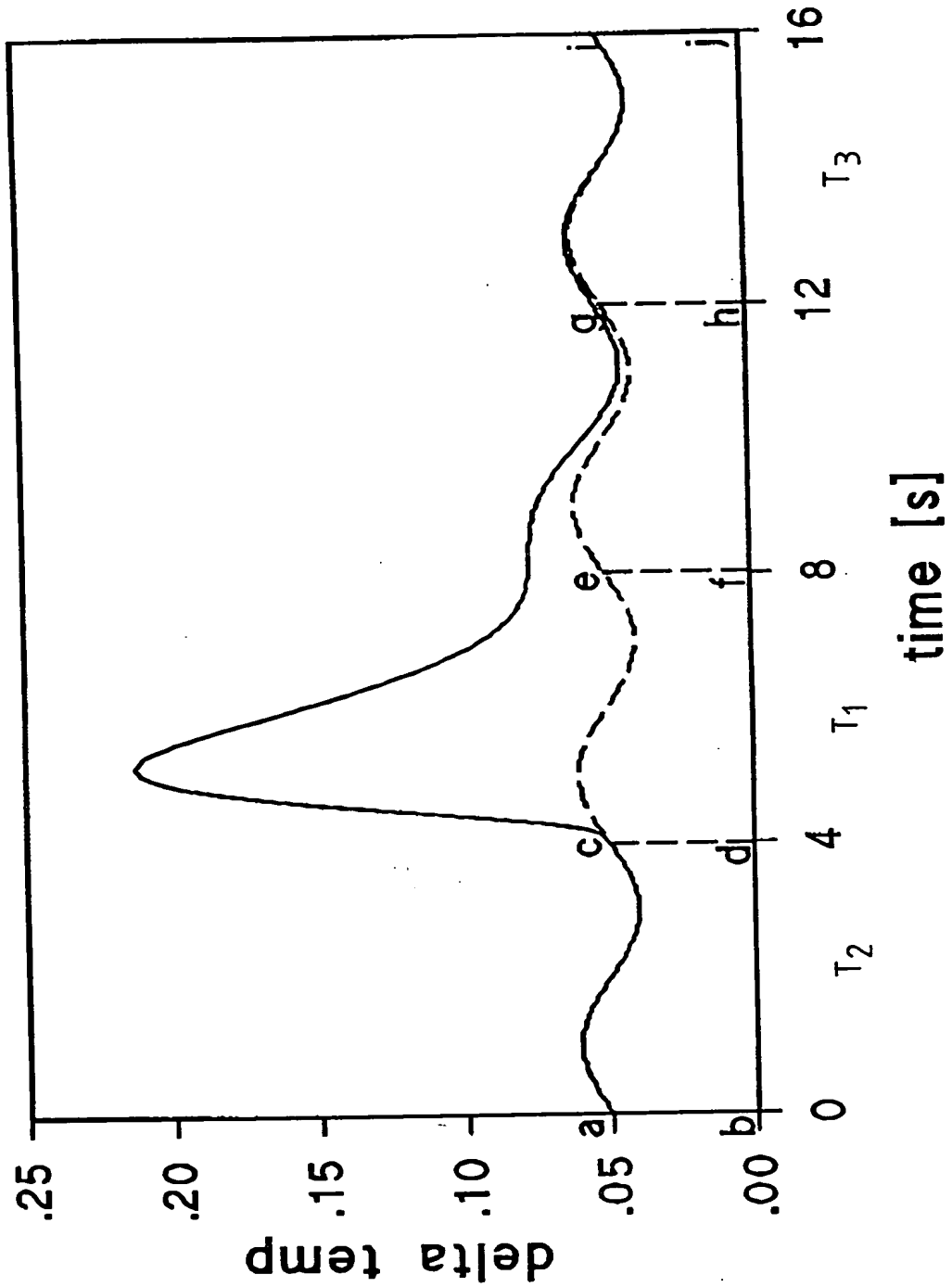

fig.2

PCT/NL 00/00102

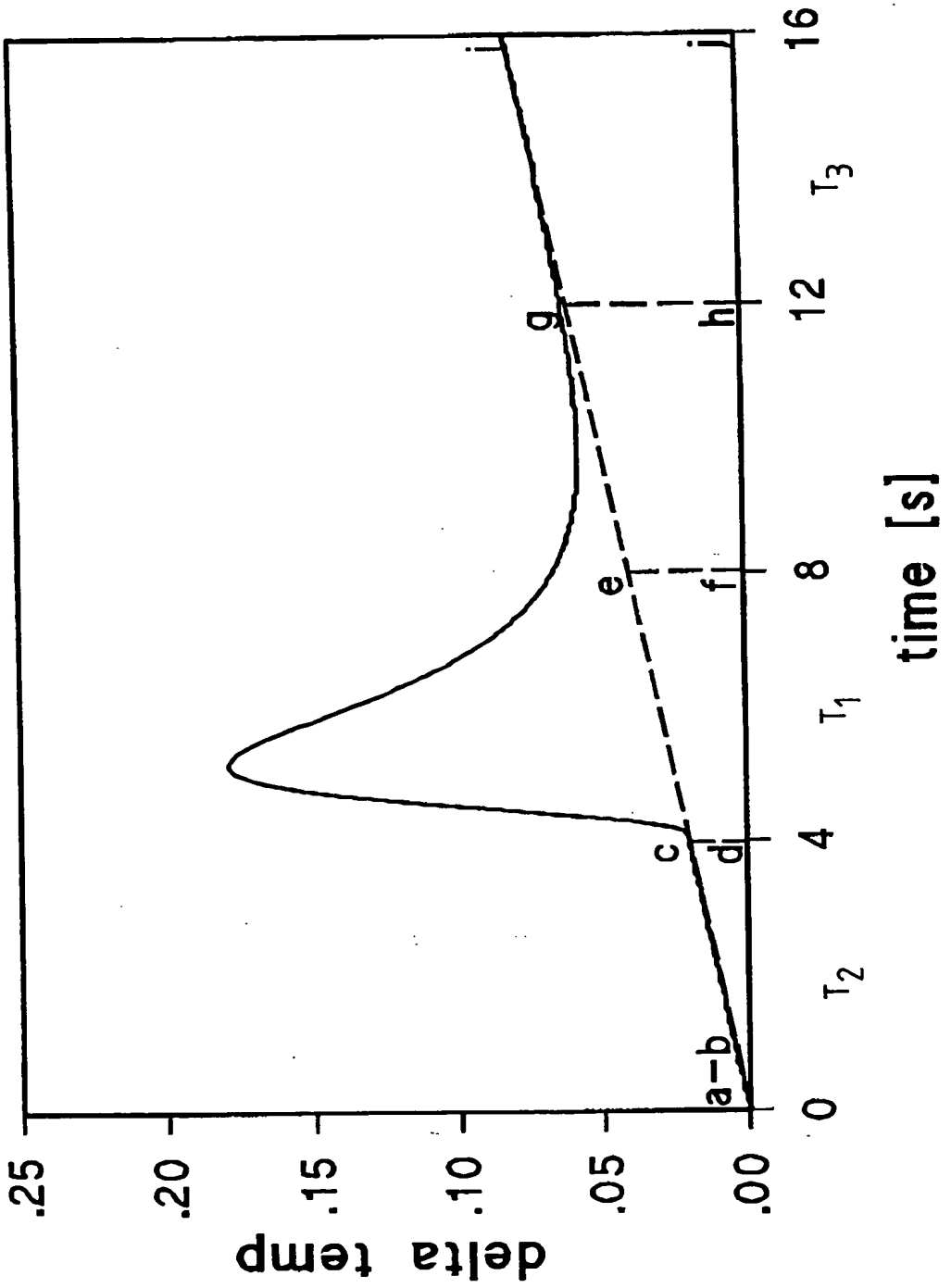

fig.3

WO3100-dV/jdh

Werkwijze en inrichting voor het bepalen van de bloedstroomsterkte van het hart van een patiënt

De uitvinding heeft betrekking op een werkwijze voor het bepalen van de bloedstroomsterkte van het hart van een patiënt, waarbij de ademhalingscyclus van de patiënt wordt bepaald en een indicator in de bloedbaan van de patiënt wordt geïnjecteerd gedurende althans nagenoeg één ademhalingscyclus, waarbij het verloop van de indicatorwaarde in de bloedbaan stroomafwaarts van de injectieplaats wordt gemeten over een aantal (n) ademhalingscycli en de geïnjecteerde hoeveelheid indicator wordt vastgesteld, waarbij uit het gemeten verloop van de indicatorwaarde, de geïnjecteerde hoeveelheid en de beginwaarde van de indicator de bloedstroomsterkte wordt bepaald, alsmede op een inrichting voor het bepalen van de bloedstroomsterkte van het hart van een patiënt.

De volgens deze werkwijze uitgevoerde meting staat bekend als een thermo-dilutiemeting, waarbij een catheter in de bloedbaan van de patiënt wordt ingebracht, via welke als indicator bijvoorbeeld een relatief koude vloeistof in het bloed wordt geïnjecteerd. Op dezelfde of een soort gelijke catheter is in de stromingsrichting van het bloed gezien stroomafwaarts van de injectieplaats een detector aangebracht, waarmee de temperatuur in het bloed kan worden gemeten. Op deze wijze kan een zogenaamde thermo-dilutiecurve worden bepaald, die het verloop van de temperatuur aangeeft. Aangezien de geïnjecteerde indicator hoeveelheid bekend is, kan uit de thermo-dilutiecurve de bloedstroomsterkte van het hart worden bepaald. Bij de bekende werkwijze geldt als voorwaarde dat de bloedstroomsterkte van het hart constant is. In de praktijk is evenwel gebleken, dat twee belangrijke verstoringen van de constant veronderstelde bloedstroomsterkte bestaan; enerzijds is dit de pulserende stroomsterkte ten gevolge van de hartactie en anderzijds alle andere laagfrequente variaties in de stroomsterkte, die bijvoorbeeld worden veroorzaakt door beademing van de patiënt. De

stroomsterktevariaties ten gevolge van de hartactie worden in het algemeen niet als verstorend ervaren voor toepassing van de thermo-dilutiemethode. Wanneer echter een patiënt door een beademingsapparaat wordt beademd, wordt de bloedstroomsterkte zodanig beïnvloed dat deze niet meer als constant mag worden beschouwd, maar een fluctuerend karakter heeft. Juist wanneer een patiënt door een beademingsapparaat wordt beademd is een nauwkeurige bepaling van de gemiddelde bloedstroomsterkte zeer gewenst, aangezien deze waarde één van de criteria vormt voor bij het bewaken van de toestand van de patiënt. Uit onderzoekingen van onder andere J.R.C. Jansen et al, Intensive Care Med 1990, 16, blz. 422-425, is gebleken dat bij het bepalen van de bloedstroomsterkte van het hart met behulp van de thermo-dilutiemethode de meetresultaten een spreiding van 65-125% van het gemiddelde kunnen vertonen.

In NL-B-1 005 572 een werkwijze en inrichting van de bovengenoemde soort beschreven, waarmee de nauwkeurigheid van de thermo-dilutiemethode kan worden verbeterd, door de indicator precies over één ademhalingscyclus te injecteren. Door slechts één injectie over de duur van een ademhalingscyclus toe te passen, wordt een zelfde resultaat bereikt als door het gemiddelde te berekenen van een aantal thermo-dilutiemetingen volgens de conventionele methode, zoals onder andere beschreven in het bovengenoemde artikel.

De uitvinding beoogt de werkwijze en inrichting van de in de aanhef genoemde soort verder te verbeteren.

Hiertoe heeft de werkwijze volgens de uitvinding het kenmerk dat een eerste variatie van de indicatorwaarde wordt gemeten over althans nagenoeg één ademhalingscyclus bij voorkeur direct voorafgaand aan de injectie en het verloop van de indicatorwaarde wordt bepaald uit het verschil van het gemeten indicatorwaardeverloop over een periode van n maal die van de eerste variatie en n maal de gemeten eerste variatie.

Op deze wijze wordt de nauwkeurigheid van de thermo-dilutiemethode verder verbeterd, doordat de variatie in de indicatorwaarde over één ademhalingscyclus wordt verwijderd uit de meting van de indicatorwaarde over n ademhalingscycli. Hierdoor wordt elke cyclische variatie van de indicatorwaarde uit

het meetresultaat verwijderd.

Bij voorkeur wordt een tweede variatie van de indicatorwaarde gemeten over althans nagenoeg één ademhalingscyclus bij voorkeur direct aansluitend op de meting van het verloop van de indicatorwaarde, waarbij het gemiddelde van de eerste en tweede variatie wordt bepaald, welk gemiddelde wordt gebruikt voor het bepalen van het verloop van de indicatorwaarde in plaats van de eerste variatie. Hierdoor wordt het voordeel bereikt, dat de nauwkeurigheid verder wordt verbeterd en tevens de invloed van langzame drift in de indicatorwaarde uit het meetresultaat wordt weggenomen.

Volgens een bijzonder gunstige uitvoeringsvorm wordt tevens een zogenaamde pulscontourmeting uitgevoerd, waarbij een arterieel bloeddruksignaal wordt gemeten. Het arteriële bloeddruksignaal is ongeveer evenredig met de bloedstroomsterkte zelf, indien wordt aangenomen dat de karakteristieke impedantie van het bloedvaatstelsel constant is. Aan deze voorwaarde wordt in de praktijk niet voldaan, omdat deze karakteristieke impedantie met een betrekkelijk grote tijdconstante varieert. Volgens de uitvinding is een nauwkeurige meting mogelijk, doordat het arteriële bloeddruksignaal wordt gemeten, waarbij over een periode overeenkomend met het aantal (n) ademhalingscycli de waarde van het slagvolume en de bloedstroomsterkte worden berekend over een hartslagperiode, waarbij het gemiddelde van de berekende waarden wordt bepaald, waarbij uit een vergelijking van de aldus berekende gemiddelde waarde van de bloedstroomsterkte en de uit het indicatorwaardeverloop bepaalde bloedstroomsterkte een evenredigheidsconstante wordt berekend, waarna met behulp van de berekende evenredigheidsconstante het slagvolume en de bloedstroomsterkte worden vermenigvuldigd. Op deze wijze wordt als het ware het resultaat van de thermodilutiemeting als ijking voor de pulscontourmeting gebruikt, waarna zonder volgende injecties door middel van de pulscontourmeting voortdurend de bloedstroomsterkte kan worden bewaakt. Desgewenst kan het bepalen van de bloedstroomsterkte uit het indicatorwaardeverloop door het uitvoeren van een nieuwe injectie en het berekenen van de evenredigheidsconstante periodiek worden herhaald.

De uitvinding verschaft tevens een inrichting voor het bepalen van de bloedstroomsterkte van het hart van een patiënt, voorzien van een verwerkingseenheid met een besturingsuitgang voor het besturen van een injectie-orgaan, een eerste detector voor het meten van het verloop van een indicatorwaarde in de bloedbaan van de patiënt en een tweede detector voor het bepalen van de ademhalingscyclus van de patiënt, waarbij de verwerkingseenheid is ingericht om het verloop van de indicatorwaarde in de bloedbaan stroomafwaarts van de injectieplaats te meten over een aantal (n) ademhalingscycli, de geïnjecteerde hoeveelheid indicator vast te stellen en uit het gemeten verloop van de indicatorwaarde, de geïnjecteerde hoeveelheid en de beginwaarde van de indicator de bloedstroomsterkte te bepalen, welke inrichting volgens de uitvinding het kenmerk heeft, dat de verwerkingseenheid is ingericht om een eerste variatie van de indicatorwaarde te meten over althans nagenoeg één ademhalingscyclus bij voorkeur direct voorafgaand aan de injectie van de indicator en het verloop van de indicatorwaarde te bepalen uit het verschil van het gemeten indicatorwaardeverloop over een periode van n maal die van de eerste variatie en n maal de gemeten eerste variatie.

De uitvinding wordt hierna nader toegelicht aan de hand van de tekening, waarin een uitvoeringsvoorbeeld van de inrichting volgens de uitvinding schematisch is weergegeven.

Fig. 1 is een blokschema van een uitvoeringsvorm van de inrichting volgens de uitvinding.

De fig. 2 en 3 tonen grafieken ter toelichting van de werkwijze volgens de uitvinding.

Opgemerkt wordt dat in het kader van de beschrijving en conclusies met de term ademhalingscyclus zowel een natuurlijke ademhalingscyclus als een beademingscyclus wordt aangeduid. Als indicator kan een koude vloeistof worden gebruikt maar ook elke andere geschikte indicator, zoals een zout- of glucose-oplossing of een kleurstof. Hoewel in het beschreven voorbeeld een koude vloeistof als indicator wordt gebruikt, kan dit derhalve ook een andere indicator zijn.

In fig. 1 is een inrichting voor het meten van de bloedstroomsterkte van het hart van een patiënt weergegeven,

die is voorzien van een verwerkingseenheid 1, die bijvoorbeeld kan zijn uitgevoerd als een PC met een geschikt programma. De verwerkingseenheid 1 is voorzien van een in/uitgang 2 voor het besturen van een schematisch aangeduid injectie-orgaan 3, waarmee een koude vloeistof in de bloedbaan van de patiënt kan worden geïnjecteerd. Hiertoe wordt op gebruikelijke wijze een thermo-dilutiecatheter in een bloedvat van een patiënt gebracht. De temperatuur van deze koude vloeistof wordt gemeten met een detector 4, die is aangesloten op een ingang 5 van een versterker 6 die is aangesloten op de verwerkingseenheid 7. Op enige afstand van de injectie-opening is de niet nader weergegeven catheter voorzien van een detector 7, waarmee de temperatuur van het bloed stroomafwaarts van de injectie-opening kan worden gemeten. De detector 7 is aangesloten op een ingang 8 van een versterker 9, waarvan het uitgangssignaal eveneens aan de verwerkingseenheid 1 wordt toegevoerd. Met behulp van de tot nu toe beschreven inrichting kan een zogenaamde thermo-dilutiecurve worden bepaald, waaruit op grond van de geïnjecteerde hoeveelheid koude vloeistof en de temperatuur van deze vloeistof de bloedstroomsterkte van het hart worden berekend. Om de gemiddelde bloedstroomsterkte te kunnen bepalen zou een aantal injecties van koude vloeistof noodzakelijk zijn. Zoals in NL-B-1 005 572 is beschreven, is het mogelijk de thermo-dilutiecurve te bepalen door slechts één injectie over de duur van één ademhalingscyclus.

Hiertoe is de beschreven inrichting voorzien van een detector 10 die via een versterker 11 op de verwerkingseenheid 1 is aangesloten. De detector 10 meet een van de ademhalingscyclus afhankelijk signaal. Een dergelijke detector kan bijvoorbeeld de kooldioxide-concentratie, de luchtstroomsterkte, de temperatuur van de ademlucht of dergelijke meten. De verwerkingseenheid 1 bestuurt nu het injectie-orgaan 3 zodanig, dat één injectie van indicator wordt uitgevoerd precies over de duur van één ademhalingscyclus en legt vervolgens gedurende een aantal n ademhalingscycli het concentratieverloop van de indicator vast.

In fig. 2 is een temperatuur/tijdgrafiek weergegeven, waarin de temperatuurverandering als funktie van de tijd is

uitgezet. Door één gecontroleerde injectie over de duur van een ademhalingscyclus, wordt direct de gemiddelde bloedstroomsterkte gemeten en is het niet nodig een aantal metingen uit te voeren. In fig. 2 is de periode waarover het concentratieverloop wordt vastgelegd, aangeduid met T1. Deze periode loopt van t=4 tot t=12.

Bij een injectie van koude als indicator kan de volgende vergelijking geschreven worden

$$Q_i \rho_i S_i (T_b\ T_i) = Q'_b \rho_b S_b \int \Delta T_b(t) dt$$

waarin Q_i het injectie volume, ρ de soortelijke warmte en S de soortelijke massa van (i) injectaat en (b) bloed respectievelijk, T temperatuur, Q'_b bloedstroomsterkte en ΔT_b de verandering in temperatuur van het bloed door de injectie van koude vloeistof.

Herschikking van de formule laat zien hoe de bloedstroomsterkte berekend kan worden.

$$Q'_b = Q_i \frac{\rho_i S_i (T_b T_i)}{\rho_b S_b \int \Delta T_b(t) dt}$$

Deze formule vormt de basis voor de meeste thermodilutie "cardiac output" computers.

Uit onderzoek is gebleken, dat op deze wijze geen nauwkeurige meetresultaten kunnen worden bereikt, aangezien de pulserende stroomsterkte van het hart een fluctuerend karakter heeft ten gevolge van de ademhaling of beademing via een ventilator. Dit is schematisch weergegeven in fig. 2. In het verloop van de temperatuur zit in dit geval ook
een temperatuurvariatie, die niet wordt veroorzaakt door de injectie. Deze variatie wordt veroorzaakt door de ademhaling. Deze invloed van de ademhaling kan worden verwijderd, door het oppervlak onder de gemeten temperatuurcurve over precies één ademhalingscyclus te meten, bij voorkeur onmiddellijk voordat de injectie van de koude vloeistof plaatsvindt. Bij het in fig. 2 weergegeven voorbeeld vindt de injectie plaats op t=4 en

wordt derhalve eerst het oppervlak over de periode T2 gemeten. Op het tijdstip van de injectie t=4 start de bepaling van het oppervlak onder de temperatuurcurve gedurende een heel aantal n ademhalingscycli tot t=12. Het oppervlak tengevolge van de injectie van de koude vloeistof is dan Area-Dil = B - n x A.

De bloedstroomsterkte wordt vervolgens berekend als:

$$Q'_b = Q_i \frac{\rho_i S_i (T_b T_i)}{\rho_b S_b . Area - Dil}$$

Voorts kan de invloed van langzame temperatuurdrift tengevolge van bijvoorbeeld verhoging of verlaging van de lichaamstemperatuur worden geëlimineerd, door zowel direct voor als direct na de injectie het temperatuurverloop over precies één ademhalingscyclus te meten. Deze situatie is in fig. 3 weergegeven. Hierbij wordt zowel het oppervlak in de periode T2 als het oppervlak in de periode T3 gemeten, zodat het oppervlak tengevolge van de injectie van de koude vloeistof wordt Area-Dil = B - n/2 x (A + C).

Met de beschreven inrichting en werkwijze kan derhalve de gemiddelde bloedstroomsterkte van het hart van een patiënt met hoge nauwkeurigheid worden gemeten door slechts één injectie van indicator.

Volgens een bijzonder gunstige uitvoeringsvorm wordt de inrichting tevens voorzien van een detector 12 die via een versterker 13 op de verwerkingseenheid 1 is aangesloten. De detector 12 meet het arteriële bloeddruksignaal, bij voorbeeld in de lichaamsslagader. Het is op zichzelf bekend, dat uit dit arteriële bloeddruksignaal over één hartslag de niet gekalibreerde waarde van het slagvolume en de bloedstroomsterkte kan worden berekend. Dit is bijvoorbeeld beschreven in US-A-3 841 313. Bij de beschreven inrichting worden over de tijdsduur van de meting van de thermo-dilutiecurve de berekende waarden van de bloedstroomsterkte vastgelegd en wordt hiervan het gemiddelde bepaald. Door de aldus berekende waarde van de bloedstroomsterkte met de bloedstroomsterkte die door middel van de thermo-dilutiemethode is bepaald, wordt vervolgens door de verwer-

kingseenheid 1 een evenredigheidsconstante berekend. Vervolgens kunnen continue de berekende waarden voor het slagvolume en de bloedstroomsterkte die volgen uit het meten van de artriële bloeddruk met behulp van deze evenredigheidsconstante in nauwkeurige meetwaarden omgezet.

Desgewenst kan de verwerkingseenheid zo zijn geprogrammeerd, dat periodiek een thermo-dilutiebepaling op de beschreven wijze wordt uitgevoerd en kan een nieuwe evenredigheidsconstante worden vastgesteld.

Opgemerkt wordt dat de meetresultaten desgewenst op een beeldscherm 13 zichtbaar kunnen worden gemaakt. Voorts wordt opgemerkt, dat de thermo-dilutiemeting automatisch kan worden gestart dan wel door middel van het geven van een geschikt commando via bijvoorbeeld een toetsenbord 14.

De uitvinding is niet beperkt tot het in het voorgaande beschreven uitvoeringsvoorbeeld, dat binnen het kader der conclusies op verschillende manieren kan worden gevarieerd.

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CONCLUSIES

1. Werkwijze voor het bepalen van de bloedstroomsterkte van het hart van een patiënt, waarbij de ademhalingscyclus van de patiënt wordt bepaald en een indicator in de bloedbaan van de patiënt wordt geïnjecteerd gedurende althans nagenoeg één ademhalingscyclus, waarbij het verloop van de indicatorwaarde in de bloedbaan stroomafwaarts van de injectieplaats wordt gemeten over een aantal (n) ademhalingscycli en de geïnjecteerde hoeveelheid indicator wordt vastgesteld, waarbij uit het gemeten verloop van de indicatorwaarde, de geïnjecteerde hoeveelheid en de beginwaarde van de indicator de bloedstroomsterkte wordt bepaald, met het kenmerk, dat een eerste variatie van de indicatorwaarde wordt gemeten over althans nagenoeg één ademhalingscyclus bij voorkeur direct voorafgaand aan de injectie en het verloop van de indicatorwaarde wordt bepaald uit het verschil van het gemeten indicatorwaardeverloop over een periode van n maal die van de eerste variatie en n maal de gemeten eerste variatie.

2. Werkwijze volgens conclusie 1, waarbij een tweede variatie van de indicatorwaarde wordt gemeten over althans nagenoeg één ademhalingscyclus bij voorkeur direct aansluitend op de meting van het verloop van de indicatorwaarde, waarbij het gemiddelde van de eerste en tweede variatie wordt bepaald, welk gemiddelde wordt gebruikt voor het bepalen van het verloop van de indicatorwaarde in plaats van de eerste varatie.

3. Werkwijze volgens conclusie 1 of 2, waarbij het arteriële bloeddruksignaal wordt gemeten, waarbij over een periode overeenkomend met het aantal (n) ademhalingscycli de waarde van het slagvolume en de bloedstroomsterkte worden berekend over een hartslagperiode, waarbij het gemiddelde van de berekende waarden wordt bepaald, waarbij uit een vergelijking van de aldus berekende gemiddelde waarde van de bloedstroomsterkte en de uit het indicatorwaardeverloop bepaalde bloedstroomsterkte een evenredigheidsconstante wordt berekend, waarna met behulp van de berekende evenredigheidsconstante het slagvolume en de bloedstroomsterkte worden vermenigvuldigd.

4. Werkwijze volgens conclusie 3, waarbij het bepalen van de bloedstroomsterkte uit het indicatorwaardeverloop door het uitvoeren van een nieuwe injectie en het berekenen van de eveneredigheidsconstante periodiek worden herhaald.

5. Inrichting voor het bepalen van de bloedstroomsterkte van het hart van een patiënt, voorzien van een verwerkingseenheid met een besturingsuitgang voor het besturen van een injectie-orgaan, een eerste detector voor het meten van het verloop van een indicatorwaarde in de bloedbaan van de patiënt en een tweede detector voor het bepalen van de ademhalingscyclus van de patiënt, waarbij de verwerkingseenheid is ingericht om het verloop van de indicatorwaarde in de bloedbaan stroomafwaarts van de injectieplaats te meten over een aantal (n) ademhalingscycli, de geïnjecteerde hoeveelheid indicator vast te stellen en uit het gemeten verloop van de indicatorwaarde, de geïnjecteerde hoeveelheid en de beginwaarde van de indicator de bloedstroomsterkte te bepalen, met het kenmerk, dat de verwerkingseenheid is ingericht om een eerste variatie van de indicatorwaarde te meten over althans nagenoeg één ademhalingscyclus bij voorkeur direct voorafgaand aan de injectie van de indicator en het verloop van de indicatorwaarde te bepalen uit het verschil van het gemeten indicatorwaardeverloop over een periode van n maal die van de eerste variatie en n maal de gemeten eerste variatie.

6. Inrichting volgens conclusie 5, waarbij de verwerkingseenheid is ingericht om een tweede variatie van de indicatorwaarde te meten over althans nagenoeg één ademhalingscyclus bij voorkeur direct aansluitend op de meting van het verloop van de indicatorwaarde, waarbij de verwerkingseenheid het gemiddelde van de eerste en tweede variatie bepaalt, welk gemiddelde wordt gebruikt voor het bepalen van het verloop van de indicatorwaarde in plaats van de eerste varatie.

7. Inrichting volgens conclusie 5 of 6, voorzien van een derde detector voor het bepalen van een arterieel bloeddruksignaal, waarbij de verwerkingseenheid is ingericht om over een periode overeenkomend met het aantal (n) ademha lingscycli de waarde van het slagvolume en de bloedstroomsterkte te berekenen over een hartslagperiode, waarbij het gemiddelde van de

berekende waarden wordt bepaald, waarbij de verwerkingseenheid de aldus berekende gemiddelde waarde van de bloedstroomsterkte en de uit het indicatorwaardeverloop bepaalde bloedstroomsterkte vergelijkt en een evenredigheidsconstante berekent, waarna de verwerkingseenheid het slagvolume en de bloedstroomsterkte, die uit het arteriële bloeddruksignaal worden berekend, vermenigvuldigt met de berekende evenredigheidsconstante.

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UITTREKSEL

Voor het bepalen van de bloedstroomsterkte van het hart van een patiënt wordt de ademhalingscyclus van de patiënt bepaald en wordt een indicator in de bloedbaan van de patiënt geïnjecteerd gedurende althans nagenoeg één ademhalingscyclus. Het verloop van de indicatorwaarde in de bloedbaan stroomafwaarts van de injectieplaats wordt gemeten over een aantal ademhalingscycli (n) en de geïnjecteerde hoeveelheid indicator wordt vastgesteld. Uit het gemeten verloop van de indicatorwaarde, de geïnjecteerde hoeveelheid en de beginwaarde van de indicator wordt de bloedstroomsterkte bepaald. Hiertoe wordt een eerste variatie van de indicatorwaarde gemeten over althans nagenoeg één ademhalingscyclus direct voorafgaand aan de injectie en wordt het verloop van de indicatorwaarde bepaald uit het verschil van het gemeten indicatorwaardeverloop over een periode van n maal die van de eerste variatie en n maal de gemeten eerste variatie.